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Medical Staff Conference

Choriocarcinoma and Gestational Trophoblastic Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic of Medical Grand Rounds this morning is choriocarcinoma and gestational trophoblastic disease. We have asked Dr. Michael Friedman of our Cancer Research Institute to discuss this relatively uncommon disorder.*

DR. FRIEDMAN:† For centuries physicians have studied gestational trophoblastic diseases with increasing interest. Perhaps the first written description of a molar pregnancy was offered by Hippocrates (Aphorisms 1.45): "When women, in a moderate condition of body, miscarry in the second or third month, without any obvious cause, their cotyledones are filled with mucosity, and cannot support the weight of the fetus, but are broken asunder." Today, tumors of this family of diseases are of interest not merely because they are neoplasms responsive to chemotherapy, but also because they represent an almost ideal model system for the general study of malignant disease. Focusing on gestational trophoblastic disease, we confront questions of cellular growth and differentiation that are central to human biology and embryology. Furthermore, we must deal with important immunologic issues relating to fetal and tumor antigen recognition—currently an attractive subject because of the renaissance of interest in immunotherapy. And finally, we have access to cellular kinetic information that directs rational therapy (in contrast to the usual empiric approaches).

Trophoblastic disease includes three related conditions: (1) molar pregnancy, (2) metastatic molar disease (chorioadenoma destruens) and (3) choriocarcinoma. These entities may occur as isolated diseases or one may follow another in a particular patient. Most commonly these diseases are associated with pregnancy, but their occurrence may be nongestational as well. Often choriocarcinoma occurs as a perigestational event, but it may arise as a primary tumor of the mediastinum or retroperitoneum that is unassociated with pregnancy, and when it does the prognosis will be less hopeful. The histopathologic distinctions between these tumors are crucial. Differentiation between locally invasive mole, metastatic mole and true metastatic choriocarcinoma directs the treatment regimen and predicts the response

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ABBREVIATIONS USED IN TEXT

DNA = deoxyribonucleic acid
HCG = human chorionic gonadotropin
LH = luteinizing hormone
TBG = thyroxine-binding globulin
TSH = thyroid-stimulating hormone

to therapy and the curability. It is necessary to classify each patient's disease in terms of gestational association, histopathologic criteria and extent of metastasis.

The placenta (the initial common tissue for these tumors) is composed of normal trophoblastic elements. Viewed microscopically it evidences cellular pleomorphism, vascular invasion and nuclear atypia. Recognizing the usual biologic activity of a placenta (aggressive local encroachment and early vascular invasion), one wonders why it is not commonly considered a malignant tissue. More provocative perhaps is the fact that during pregnancy, and especially at the time of delivery, a large volume of placental tissue is deported from the pelvis to the pulmonary vasculature. This phenomenon, except when it is noticed during the occasional attendant cardiovascular or hemostatic problem, is clinically unrecognized. Rarely is placental tissue radiologically evident in the maternal lungs after a delivery. What is it about placental tissue that makes it unique among normal tissues and confers on it some malignant characteristics? Perhaps investigating the normal trophoblast provides some insight into why malignant trophoblastic disease has the potential for growth and spread and why it responds to treatment the way it does. Trophoblastic growth may be thought of as points on a continuum ranging from a benign state (normal placental tissue) through more malignant states (molar pregnancy and metastatic mole or chorioadenoma destruens), to the most malignant situation, choriocarcinoma. All of these display similar cellular elements (elements in common with normal trophoblastic tissue), and they all share the same repertoire of elaborated hormones.

Hydatid mole is easily recognized grossly, and pathophysiologically it represents massive hydropic degeneration of the villi (an overt failure of the maternal and fetal vessels to join properly, and with villi that are still microscopically clearly visible). That this condition is relatively uncommon in the United States should in no way influence our perspective of the worldwide impact of this disease. In Formosa, parts of Southeast Asia and Central America it is a common problem, and is present in almost 1 percent of the pregnancies observed. In the United States only between one in 1,000 and one in 3,000 pregnancies are molar in nature.[1] Moles can be seen as either locally invasive or distantly metastatic. Since a local or metastatic mole is easier to treat and cure than a choriocarcinoma, the distinction between them is a crucial one. Choriocarcinoma, whether it is locally present or widely metastatic, is the most malignant member of this family, and it is the most difficult to treat. Microscopically, choriocarcinoma lacks villous structure, differentiating it from molar disease. This tumor can be widely aggressive and involve most of the organs of the body. The single most common location for metastatic spread is the lung (70 percent in most series). Local genital tract involvement is fairly common (20 to 30 percent), and probably results from direct spread at the time of evacuation or curettage.[2] Virtually any organ system can be affected, but perhaps the most significant site is the central nervous system, where metastases are of dire consequence. In considering the diagnosis of choriocarcinoma in a patient, one must histologically confirm a metastatic nodule in order to initiate a proper therapy.

The association of choriocarcinoma with molar pregnancy is well recognized but the two are not always connected; and at the time of diagnosis of a mole it is impossible to predict what malignant sequelae, if any, will follow. Even in normal pregnancy subsequent choriocarcinoma is sometimes seen. Focal dysplastic or neoplastic sites are probably present in normal placenta; but the technical difficulties one encounters in scanning several square meters of normal placental tissue to look for such tiny areas makes this procedure unrewarding. Possibly many of the placentae that are considered normal have microscopic abnormalities that are not detected by gross techniques. Consequently, the incidence of abnormalities is underestimated. Malignant trophoblastic sequelae are noted in 10 to 20 percent of women who have molar pregnancy. About two thirds of this group (or approximately 10 percent of those with molar pregnancies) will have either locally invasive or metastatic molar tissue. About one third (approximately 5 percent of the entire group) will have frank choriocarcinoma. Alternatively though, almost half of patients who have choriocarcinoma have not had an associated, documented preg-

nancy. Some choriocarcinomas arise in nongestational areas (mediastinum or retroperitoneum); but perhaps there are abortions that are spontaneous, missed or not reported to physicians in which unrecognized choriocarcinomatous elements are present.

In a patient who has had a molar pregnancy and subsequently presents with pulmonary nodules, a lung biopsy should be done to determine whether this tissue is composed of villous elements and therefore is metastatic mole, or whether it has none of these elements and represents choriocarcinoma, a much more serious disease.

These trophoblastic tumors are intriguing because of their biochemical and endocrinologic uniqueness. The large repertoire of products elaborated by normal and malignant trophoblastic tissues include steroids (progesterone and estrogenic compounds), protein hormones (human chorionic gonadotropin, thyrotropin and placental lactogenic hormone) and probably a variety of other products which have not as yet been completely identified. Human chorionic gonadotropin (HCG) is the tumor product of biologic and clinical significance. HCG is a glycoprotein of two subunits, an alpha and beta chain. The alpha chain is structurally similar to that of luteinizing hormone (LH) and to thyroid-stimulating hormone (TSH). This similarity is probably responsible for the striking high thyroxine (T_4) levels seen in some patients with mole and choriocarcinoma (an issue separate from that of the physiologic increase in thyroxine-binding globulin [TBG]). Interestingly though, these high T_4 levels are rarely, if ever, associated with clinically prominent hyperthyroidism. The second chain of this glycoprotein, the beta subunit, provides the antigenic uniqueness to HCG. The beta subunit permits a radioimmunoassay which specifically and sensitively detects HCG (with little overlap with luteinizing hormone). The pregnancy test, as it is commonly carried out, indicates grossly elevated HCG levels, but probably 30 percent of women with choriocarcinoma and elevated levels of HCG are not identified by the common pregnancy test. There are a variety of other tests to sensitively detect HCG titers, the most specific of which is evaluation of the beta subunit HCG by radioimmunoassay.

After termination of a normal pregnancy a predictable decrease in HCG titer levels occurs, and by the eighth postpartum week these values are in the normal range of physiologic luteinizing hormone secretion. However, about one fifth of patients with molar pregnancy continue to have an elevated HCG titer at eight weeks after their curettage or abortion, and in approximately one half to three quarters of that subgroup further malignant sequelae develop. Clearly then, it is necessary to obtain follow-up serial HCG titer studies (preferably of specific beta subunit HCG titers) on all women with molar pregnancies. By means of these titer studies, patients at high risk can be identified and chemotherapy can be instituted at the earliest possible moment. In a study of 92 patients with active trophoblastic disease, Bagshawe noted that in only 4 patients were there urinary excretions less than 1,000 international units (IU) of HCG in 24 hours and in 16 patients they were greater than 1,000,000 IU. In most of the patients there were titers falling between these values.[1] It has been estimated that the presence of as few as 1,000 trophoblastic cells can be detected by specific beta subunit assays, and this clinical sensitivity is unparalleled in oncology. No other tumor gives us evidence of the presence of such a tiny amount of disease. The amount of myeloma protein certainly helps in judging disease activity in multiple myeloma, but it never pro-

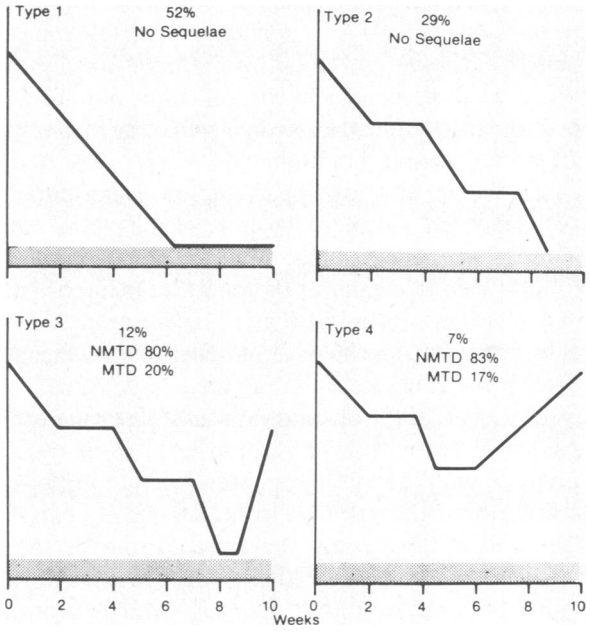

Figure 1.—Four types of gonadotropin regression slopes observed following evacuation in 116 untreated patients with molar pregnancy. Complications were limited to patients with type 3 and type 4 patterns. Percentages indicate relative frequency of nonmetastatic trophoblastic disease (NMTD) and metastatic trophoblastic disease (MTD) in each group. (Reproduced with permission from **JAMA** 220:209-213, Apr 10, 1972; Copyright 1972, American Medical Association.[1])

vides this accuracy in determining minimal tumor cellular burden. Knowing the kinetics of the HCG curve of patients who have had molar pregnancies can be of great predictive value as well. Goldstein[4] has shown (Figure 1) that in most of his patients there either was a rapid direct fall in HCG back to normal levels or a slower, steady, stair-step regression back to the normal range, with no evidence of further malignant sequelae. In contrast, in a minority of patients there were either transient near-normal levels which then rose rapidly or else persistently elevated values. In a patient in whom HCG levels are elevated, immediate intensive diagnostic study followed by therapy should be undertaken. Patients who have had molar pregnancy should be observed for several months to ensure that the normalization of this value is not a brief one but is actually a permanent one.

In evaluating patients with known or suspected metastatic choriocarcinoma, one must first define the sites of involvement of disease. Lungs and genital tract are common sites for the disease; metastases to these areas are highly responsive to therapy. Central nervous system involvement, however, has a more dire prognostic significance since intracranial bleeding is common. Patients with central nervous system involvement require both irradiation to the entire cranium and intrathecal methotrexate. The clinical status of the central nervous system can be determined by means of EMI®* scanning, radionuclide brain scan and, occasionally, arteriographic studies. Determining HCG levels in samples of cerebrospinal fluid and comparing them to those found in serum is also useful. Second, height of the HCG titer is important in evaluation of these patients. The duration of disease, judged from the time of abortion or evacuation to the time metastatic disease is detected, as well as the titer of HCG are useful prognostic guides. Women with early disease of short duration and with low titers responded well to therapy, and 95 percent appeared to be completely cured. But if the disease has progressed for over four months and the HCG titers are in excess of 1,000,000, the cure rate is much lower. The risk of death is higher with advanced disease of long duration and with a high titer. Treatment of a high-risk patient with a single drug is inadequate; multiple chemotherapeutic agents should be employed.

*Manufactured by EMI Medical, Inc., 3605 Woodhead Drive, Northbrook, IL 60062.

The chemotherapy of choriocarcinoma is a bright spot in adult malignant disease and a subject dear to the hearts of chemotherapists. There are few diseases the responses of which are so dramatically complete and predictable.

Since 1957, when methotrexate was first shown to be curative for choriocarcinoma (by Hertz and Li at the National Cancer Institute), an increasing body of information has accumulated suggesting that methotrexate is not only the standard drug, but may in fact be the primary drug for the treatment of choriocarcinoma. The unique efficacy of methotrexate in this disease may relate to the peculiar folate requirements of the pregnant mother, the fetus and the placenta. Women whose diets usually supply adequate folate become folate deficient in pregnancy. Not enough is known about the folic acid metabolism of placental tissue, but perhaps one reason methotrexate is such an effective drug is that it is a potent antifol. It has been estimated that nearly 90 percent of patients with early choriocarcinoma can be cured with methotrexate and that 40 percent of patients with more advanced disease are cured with only this single agent.[1]

In addition, a variety of other agents are effective in treating choriocarcinoma. Dactinomycin (Cosmegen®) is probably as effective as metho-

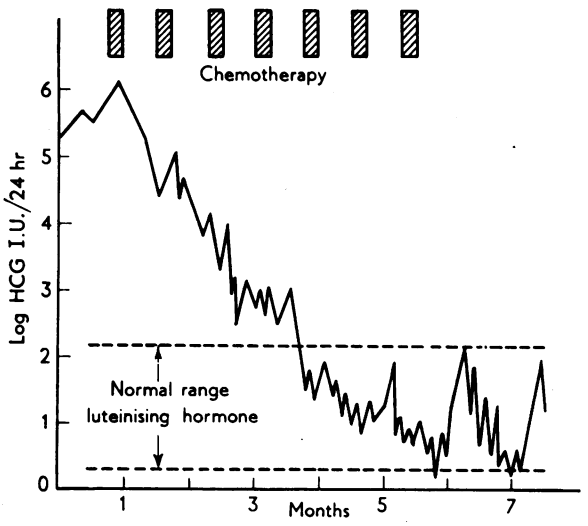

Figure 2.—The fall in human chorionic gonadotropin (HCG) excretion during treatment by chemotherapy is a more or less irregular curve as shown here. Below about 250 IU per day the contribution of luteinizing hormone to the measured gonadotropin output becomes substantial and variation in the range equivalent to 10 to 150 IU. Excretion of HCG per day may be wholly attributable to fluctuations in luteinizing hormone production. (Reproduced with permission from author and publisher, Ref. 1.)

trexate in curing early and advanced disease;[5] 6-mercaptopurine (Purinethol®) and the vinca-alkaloids, vincristine (Oncovin®) and vinblastine (Velban®) have been shown to be useful in curing early disease and in ameliorating advanced disease.[1] Combinations of these drugs have been employed in treating prognostically poor situations; 6-mercaptopurine plus methotrexate have been shown to be effective; actinomycin D together with vincristine and methotrexate in combination have been used effectively, as have combinations of actinomycin D, chlorambucil (Leukeran®), and methotrexate. In some respects, all of these therapies are similar to regimens used effectively to treat patients with testicular cancer.

Figure 2 depicts the response of one of Bagshawe's patients in whom chemotherapy pulses were given.[2] Chemotherapy was effective in destroying tumor cells. Although an initial rise in HCG associated with cellular dissolution occurred, HCG fell steadily and fairly rapidly to within normal range. One might ask why chemotherapy should be continued for several cycles past the point at which normal HCG values are noted. Within this normal range a few viable cells could occultly persist; thus, to ensure complete eradication of all tumor, therapy must be continued beyond the time of normal HCG values. A kinetic model that nicely fits this situation can be described: Clinically detectable tumor burden is 10^9 or 10^{10} cells; our ability to assess amounts of tumor less than this would not be possible if it were not for this biochemical marker. With effective therapy, a persistent fall in tumor number occurs throughout the entire period of treatment. Choriocarcinoma is a tumor with a high growth fraction (proportion of cells actively dividing), and it infrequently exhibits clinical resistance to methotrexate. It is possible, by computing and extrapolating the slope of this curve, to predict the time when the last cell should be killed (the intercept between time and 0 cells). In this way we can estimate how long the patient should be treated (Figure 3). While these theoretic considerations are portrayed as clean and obvious, the clinical situation may be more complicated and refractory. Figure 4 shows four relapses of disease. The patient was treated with a combination chemotherapy on three occasions and, on the last, hysterectomy and therapy with combination of methotrexate, 6-mercaptopurine and actinomycin D were carried out. On each occasion the patient improved. The apex of the HCG curve is progressively lower in each instance, suggesting that although the tumor volume had increased, the curve had not reached its previous height.

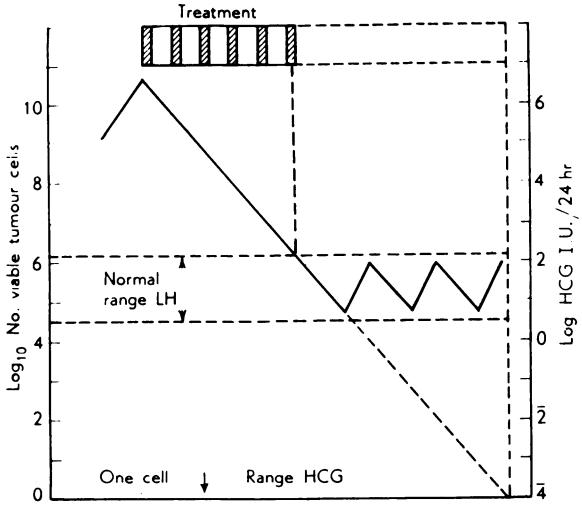

Figure 3.—By plotting a regression line through the values for human chorionic gonadotropin (HCG) excretion during treatment, the relationship between HCG excretion, normal luteinizing hormone (LH) production and the amount of hormone produced by "one cell" can be illustrated. The relationship emphasizes the need to continue treatment after normal gonadotropin values have been reached. (Reproduced with permission from author and publisher, Ref. 1.)

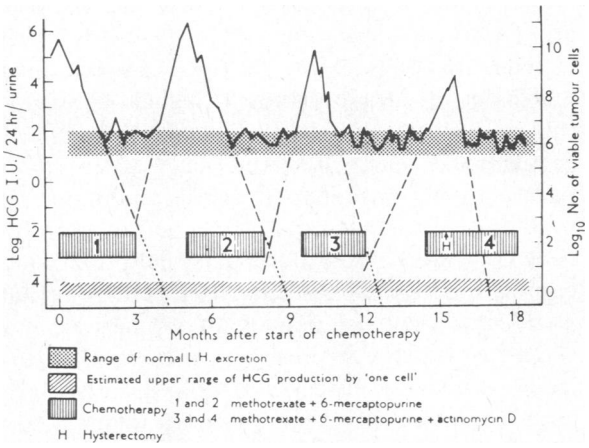

Figure 4.—Human chorionic gonadotropin (HCG) in a patient who relapsed three times after the initial response to chemotherapy. Extrapolation of the hormone descent and ascent curves from the time of completion of each series of courses of treatment is related to the estimated number of tumor cells. The first three courses of treatment were discontinued before the descent slopes intersected the "one cell" range. It should be noted that this type of analysis can be applied to only a small number of cases because the descending HCG curve is often too irregular for a useful regression line to be drawn. LH refers to leuteinizing hormone. (Reproduced with permission from author and publisher, Ref. 1.)

This case also suggests that therapy was discontinued too soon and that relapses could have been prevented by continuing therapy. The patient was eventually cured by surgical intervention and a fourth intensive course of chemotherapy. For patients with such resistant disease (for such refractory and poor-risk patients) a combination therapy is essential and offers curative potential.

The immunological aspects of this tumor are fascinating, and as a biological experiment pregnancy is an almost unparalleled phenomenon. Why is it that the fetus, a very potent antigen, is so well tolerated for the full term of pregnancy? The mother's immune response is not completely suppressed (although immunologically she is a somewhat compromised hostess), the fetal antigens are potent inducers of antibody response and the placenta is not an immunologic sanctuary. We really do not know why this foreign material is tolerated so well. It has been theorized that the infrequency of metastatic trophoblastic disease and the ease with which we cure it is somehow related to the fact that powerful immunological factors, currently incompletely identified, are at work. Several attempts to study this problem have been made. Studies of the histocompatability of placental antigens and studies in which fetal-maternal histocompatability profiles have been compared have yielded contradictory results. One group of investigators stated that in cases in which histocompatability exists, the risk of uncontrolled malignant metastatic disease is higher; but Terasaki and others have failed to make this kind of correlation. Clearly, however, some patients who have glaringly incompatible HL-A fetal-maternal profiles die of metastatic disease, and others who have compatible HL-A fetal-maternal profiles are entirely cured of disease. By itself, HL-A typing is an insufficient determinant of response.[1]

The therapeutic implications of these immunologic differences between patient and tumor have been exploited, and some ingenious immunological experiments have been carried out. Specific active immunization by means of a variety of agents has been attempted to promote immunologic rejection of the tumor. Anti-husband sperm antibodies have been injected intravenously into the affected woman, the husband's skin has been grafted onto the affected woman and leukocytes from the husband have been injected intravenously. Some nonspecific approaches, such as bacillus Calmette-Guerin (BCG) immunization and transfer factor injections have been attempted as well. Some patients may have benefited from these trials; but to date, evidence of benefit is equivocal and these procedures must be regarded as purely investigational.

A related immunologic issue, the role of HCG in the enhanced malignant potential of choriocarcinoma, requires further investigation. A growing body of evidence suggests that HCG is a potent immunosuppressive agent itself. Laboratory animals given high doses of HCG are less able to reject tumor burden and are more susceptible to particular bacterial infections. The finding that women who receive HCG (for example, for attempted weight control) show depressed humoral and cellular immunity is even more relevant and may offer a partial explanation for the association between high titers of HCG and poor prognosis. A vicious spiral can be envisioned with the development of high HCG levels, increasing tumor burden, less ability to reject the tumor and progressive disease. Other products of the trophoblast (progesterone, for example) may act similarly.

One of the thorniest issues in the treatment of malignant trophoblastic disease is the place of prophylactic therapy for patients with molar pregnancies. Early disease is easily treated and curable; the longer the duration of disease and the greater the amount of involvement, the less the chance of complete cure. If there is a therapy which is effective and reasonably safe, should all patients who have molar pregnancy receive adjunctive chemotherapy as a prophylactic measure at the time of preliminary evaluation? There is no single answer to this question; a physician must elect either to observe the patient carefully or to initiate chemotherapy immediately. No matter which course is chosen, all patients should be meticulously examined weekly. Serial HCG titers should be accurately and reproducibly carried out and any changes on x-ray films of the chest noted. If a patient can be watched in this way, if she is reliably compliant and if the physician has at his disposal proper laboratory support, then vigilance is an appropriate course to follow.

When a physician elects to withhold chemotherapy from a patient after termination of molar pregnancy, he or she must follow this type of protocol. Specific beta subunit determination should be done when the HCG levels are near physiologic range and overlap with LH. The indications for chemotherapy are unequivocal. Persistent HCG titers after 6 to 8 weeks, or plateauing or rising HCG titer indicate persistent or meta-

static disease. For complete restaging x-ray study of the chest and brain scan should be carried out, and single- or multiple-agent therapy should be administered promptly.

The alternative of immediate chemotherapy may be elected. Some investigators, however, have raised objections to the routine prophylactic treatment of molar pregnancy. First, most patients who are primarily treated surgically, or who have an abortion, are cured; and it is only in 20 to 25 percent of patients that malignant sequelae later develop. Therefore, routine adjuvant therapy would treat patients who might not need it. Second, although it must be noted that 10 to 20 percent of patients die of progressive disease, most patients in whom malignant sequelae develop in the postevacuation period can be cured. Third, minimal drug toxicity is the rule but exceptional toxicity is occasionally noted. However, methotrexate administered twice weekly is effective and causes minimal toxicity. Fourth, young women of reproductive age exposed to mutagens may suffer consequences of tetratogenic damage or may incur an enhanced risk of neoplastic disease themselves. The same risks are probably present with the use of actinomycin D and radiotherapy, which are known to intercalate with or change deoxyribonucleic acid (DNA). However, much evidence exists to suggest that methotrexate is a safer and less mutagenic agent than some other drugs might be in this type of situation.

An adjuvant regimen of proved efficacy is the use of methotrexate, 0.6 mg per kg of body weight given intramuscularly twice weekly for three weeks (six doses). In a comparative trial by Holland, women with evacuated molar pregnancies received either placebo or twice-weekly methotrexate. In eight of 65 patients randomly assigned to treatment with placebo, there were malignant sequelae. In none of the 55 patients treated with methotrexate twice weekly was there evidence of malignant progression, and in these patients there was no significant hepatic or hematologic toxicity. As expected, most of the placebo-treated patients in whom progressive malignancy occurred were subsequently successfully treated.[6]

Long ago, Hippocrates captured the essence of the dilemma posed by the treatment of this disease: ". . . the occasion fleeting, experience fallacious, and judgment difficult. The physician must not only be prepared to do what is right himself, but also make the patient, the attendants, and externals cooperate." (Aphorisms 1.1)

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